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Ancestral-derived effects on the mutational landscape of laryngeal cancer

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ABSTRACT

Laryngeal cancer disproportionately affects more African-Americans than European-Americans. Here, we analyze the genome-wide somatic point mutations from the tumors of 13 African-Americans and 57 European-Americans from TCGA to differentiate between environmental and ancestrally-inherited factors. The mean number of mutations was different between African-Americans (151.31) and European-Americans (277.63). Other differences in the overall mutational landscape between African-American and European-American were also found. The frequency of C > A, and C > G were significantly different between the two populations (p-value < 0.05). Context nucleotide signatures for some mutation types significantly differ between these two populations. Thus, the context nucleotide signatures along with other factors could be related to the observed mutational landscape differences between two races. Finally, we show that mutated genes associated with these mutational differences differ between the two populations. Thus, at the molecular level, race appears to be a factor in the progression of laryngeal cancer with ancestral genomic signatures best explaining these differences.

1. Introduction

Laryngeal cancer afflicts approximately 12,000 new individuals in the United States each year [1,2] with different incidence and survival rates across ethnic groups [1]. This particular cancer type affects more African-American (Afr-Amr) individuals than European-Americans (Eur-Amr) [1] and the five year survival rate for Afr-Amr with laryngeal cancer is consistently lower than that for Eur-Amr [1]. While socio-economic factors and life styles are associated with the higher incidence and lower survival rates among Afr-Amr [3], we have shown that the contribution of an individual's genetics cannot be ignored [4].

The major risk factors for laryngeal cancer are tobacco smoke and alcohol consumption [5,6]. Pro-carcinogens found in tobacco smoke are absorbed by cells, metabolized to form active carcinogens, and subsequently excreted from the body following detoxification [7]. If the active carcinogens are not excreted from the cell, the carcinogenic compounds may bind to and ultimately damage DNA [7]. The effect of alcohol with tobacco is synergistic; it is hypothesized that alcohol accelerates the absorption and action of tobacco-based carcinogens [8]. Defects in the enzyme activity or metabolic pathway of tobacco metabolism may lead to the accumulation of tobacco carcinogens in the body and increase the risk of tumor progression. Higher levels of nicotine and cotinine (the major nicotine-based metabolite that contributes to cancer development) have been reported in Afr-Amr compared to individuals of European descent, irrespective of smoking levels [9–12]. In addition, reduced metabolic clearance of nicotine to cotinine and decreased excretions of nicotine and cotinine have been observed in Afr-Amr, relative to Caucasians, for similar cigarette consumption [11,12]. Genetic studies have identified gene variants associated with reduced rates of nicotine metabolism in populations with significant African descent [13–15]. African-ancestry related genetic variants associated with susceptibility to cancer chemotherapeutic agents have also been demonstrated [16]. In addition, genetic variants associated with increased risk for head and neck cancers in patients of African descent have also been revealed by meta-analysis [17]. These evidences suggest the possible role of genetic ancestry, together with other non-genetic factors, in increased laryngeal cancer risk and poor survival rate among Afr-Amr. Nevertheless, genome-wide analysis to address the disparity issues in laryngeal cancer has

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